REMARKS

Claims 1-7 and 19 are currently pending. Claim 7 has been amended. The amendment to claim 7 does not constitute new matter.

Claim 19 has been allowed.

The Examiner has rejected claims 1-7 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner has rejected claims 1-7 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. For the reasons detailed below, the rejections should be withdrawn and the claims allowed to issue.

Claims 1-7 are Definite

The Examiner has rejected claims 1-7 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner states that "'activated T-lymphocytes' is unclear because one does not know what the T-lymphocytes have been activated by." The Examiner asserts that because there are "numerous art known activators of T-cells... the nature of the assaying step b) is unclear."

Applicants submit that the claims are definite because a person or ordinary skill in the art can understand the metes and bounds of the claim without needing to know what the T-lymphocytes are activated by. In order to address whether the present invention provides sufficient information regarding antigen specificity, the role of each assay must be examined. Applicants first note that the present invention is directed to *predicting the likelihood* of transplantation rejection prior to transplantation; it is not directed to determining the antigens responsible for a particular instance of transplantation rejection after the fact. See specification at page 8, lines 2-10. The role of the LGA in the present invention is to measure the amount of activated T-cells in the potential recipient, which is a gauge of the recipient's potential immune

response to the donor tissue. See specification at page 3, lines 16-17. Accordingly, the LGA is not directed to *what* the T-lymphocytes are activated by, but *whether they are activated at all.* See the specification at page 9, line 29 to page 10, line 10. It is well known in the art that activated T-lymphocytes mediate immune responses. A person of ordinary skill in the art would understand that the presence of activated T-lymphocytes, as identified by the LGA, merely indicates that the recipient host possesses an active immune system which has the potential to reject donor tissue. As transplantation rejection is thought to be related to an immune response to the donor's major histocompatibility complex (MHC) antigens, it is the HLA-DR matching and anti-HLA IgG testing steps which provide information regarding antigen-specificity, *i.e.*, these steps identify antigens which may initiation an immune response and antibodies which can mediate that response. See specification at page 1, line 13 to page 2, line 4. Thus, it is not necessary to know what the lymphocytes identified in the LGA step are activated by, because the identification of HLA-DR mismatches and anti-HLA IgG in the remaining steps provides information regarding the *likelihood* of a lymphocyte response to HLA-DR antigens. Based upon the information provided by the all three assays, a person of ordinary skill in the art would understand the role of the LGA and the scope of the information it provides, regardless of whether or not the specific activating antigen is identified. Accordingly, a person of ordinary skill in the art would therefore understand the scope of the claimed method when viewed as a whole, and the scope of the phrase "activated lymphocyte," regardless of whether it is known what activated the lymphocyte.

Further, the specification discloses that each of the three assays provides some predictive value when used alone, but it is the combination of the three assays which provides reliable predictive ability. See specification at page 12, lines 5-14. Accordingly, it is not proper to view

one of the assays used in the method without also considering the information provided by the remaining assays. See MPEP § 2173.02 ("[T]he examiner must consider the claim *as a whole* to determine whether the claim apprises one of ordinary skill in the art of its scope....") (emphasis added). The Examiner is erroneously viewing the lymphocyte growth assay (LGA) step independently from the other steps of the method. All three steps must be properly considered together; the LGA step is simply one risk factor that identifies the presence of activated T-lymphocytes, and therefore the presence of a responsive immune system. See specification at page 26, lines 1-11. The HLA-DR matching and anti-HLA IgG testing are additional risk factors which indicate the presence of potential antigens (mismatched HLA-DR) and antibodies (anti-HLA-IgG), which may initiate and/or mediate the immune response. *Id.*; see also specification at page 1, line 13 to page 2, line 4. Accordingly, to properly assess whether sufficient information regarding antigen specificity is provided, all three assays must be considered together.

The Examiner also asserts that claim 7 is indefinite due to the phrase "the presence of antigen activated lymphocytes" because there is no antecedent basis for "antigen activated" or what the "antigen" is. Without making any concessions, Applicants note that claim 7 has been amended to delete the term "antigen." Accordingly, Applicants submit that this ground of rejection has been obviated.

Based upon the foregoing remarks, Applicants submit that the Examiner's rejections have been overcome and that claims 1-7 are definite. Applicants respectfully request that the rejections be withdrawn.

Claims 1-7 are Enabled

The Examiner has rejected claims 1-7 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner states that the specification

> "does not provide enablement for [the] case in which one determines whether the T-lymphocytes of step b) have been activated by any non-specific activating agent or by any antigen.... Applicant's disclosure has only shown a correlation between a risk of transplant rejection in the case in which the T-lymphocytes of the recipient are activated against HLA-DR antigens of the doner. [*sic*] Applicant's disclosure has shown no correlation between risk of transplant rejection and presence of T-lymphocytes that have been non-specifically activated... or that have been activated by a totally unrelated antigen... or that have been activated by HLA-DR antigens that are not of the type of the donor."

The Examiner further asserts that it would require undue experimentation to determine the correlation between the risk of transplant rejection and such T-lymphocyte activation.

The claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d. at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Evaluation of undue experimentation involves, but is not limited to the following factors: breadth of the claims, nature of the invention, state of the prior art, level of one of ordinary skill, level of predictability, amount of direction provided by the inventor, existence of working examples and the quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d. at 731, 8 USPQ2d at 1400 (Fed. Cir. 1988).

Applicants assert that the specification provides sufficient disclosure to enable a person of ordinary skill in the art to make and use the invention. As noted above, the LGA step cannot be viewed in isolation, without also considering the HLA matching step and the IgG detection step. See MPEP § 2164.08 ("The focus of the examination inquiry is whether everything within the scope of the claim is enabled.... The examiner should determine what each claim recites and what the subject matter is when the claim is considered as a whole, not when its parts are

analyzed individually.") (emphasis in original). The specification provides ample disclosure that the method of the present invention works regardless of whether it is known what activated the lymphocytes, because the HLA-DR matching and anti-HLA IgG testing identify the presence of antigens that are most likely to cause transplantation rejection, *i.e.*, mismatched HLA-DR antigens. The specification provides clear directions and working examples which allow a person of ordinary skill in the art to assess the risk of transplant rejection, irregardless of the specific antigen or mitogen which is activating the lymphocytes. See page 18, line 1 to page 20, line 7 and page 23, line 8 to page 26, line 30. Although the Examiner argues that the specification does not provide any disclosure to show a correlation between the risk of transplantation rejection and T-lymphocytes activated non-specifically or by unrelated antigens, Applicants note that the examples in the specification do not disclose what the activated lymphocytes are activated by. See, for example, the specification at page 12, lines 5-29 and page 25, lines 1-30 (lymphocytes were non-specifically stimulated by IL-2 and their growth measured). Despite the apparent lack of knowledge regarding what (in specific terms) activated the lymphocytes, the examples show a high degree of reliability for predicting the likelihood of transplantation rejection. See specification at page 26, line 16 to page 27, line 2.

Furthermore, a person of ordinary skill in the art is given ample guidance to perform the method of the present invention. Indeed, individually, each of the assays of the present invention is well known in the art, and performing these assays is well within the abilities of a person of ordinary skill in the art. See MPEP § 2164.01 ("A patent need not teach, and preferably omits, what is well known in the art."). Ample guidance is also given regarding how to interpret the results of the assays. See specification at page 12, line 1 to page 14, line 23, and at page 26, line 16 to page 27, line 2. A person of ordinary skill in the art, using the assays in conjunction as

directed by the specification, will be able to reliably predict the risk of transplantation rejection, with no more than routine experimentation. Accordingly, Applicants submit that the specification provides an enabling disclosure which allows a person of ordinary skill in the art to make and use the invention..

For the foregoing reasons, Applicants respectfully request withdrawal of the rejection of claims 1-7 under 35 U.S.C. §112, first paragraph.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the inventions described and defined by claims 1-7 and 19 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the claims are requested. An early allowance is earnestly sought.

Respectfully submitted,

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